

University of Groningen

Predictors for Starting Depot Administration of Risperidone in Chronic Users of Antipsychotics

Vehof, J.; Postma, M.J.; Bruggeman, R.; de Jong-van den Berg, L.T.W.; van den Berg, P.D.; Stolk, R.P.; Burger, H.

Published in:
Journal of Clinical Psychopharmacology

DOI:
[10.1097/JCP.0b013e31818a6d10](https://doi.org/10.1097/JCP.0b013e31818a6d10)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vehof, J., Postma, M. J., Bruggeman, R., de Jong-van den Berg, L. T. W., van den Berg, P. D., Stolk, R. P., & Burger, H. (2008). Predictors for Starting Depot Administration of Risperidone in Chronic Users of Antipsychotics. *Journal of Clinical Psychopharmacology*, 28(6), 625-630.
<https://doi.org/10.1097/JCP.0b013e31818a6d10>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Predictors for Starting Depot Administration of Risperidone in Chronic Users of Antipsychotics

Jelle Vehof, MSc,*† Maarten J. Postma, PhD,*† Richard Bruggeman, PhD,†‡
Lolkje T. W. De Jong-Van Den Berg, PhD,† Paul B. Van Den Berg, MSc,†
Ronald P. Stolk, PhD,* and Huibert Burger, PhD*†

Background: Risperidone long-acting injectable (RLAI), the first second-generation depot antipsychotic, has extensively been studied before introduction. Thereafter, questions about the type of patients actually treated with RLAI in daily practice remain to be answered for making valid antipsychotic treatment comparisons involving RLAI in observational studies.

Objective: We aimed to determine in chronic antipsychotic users who switched treatment, predictors for the prescription of (1) depot versus oral antipsychotics and (2) RLAI versus first-generation antipsychotics (FGAs) depot.

Methods: We used pharmacy dispensing data from 53 community pharmacies in the northeast of the Netherlands containing approximately 500,000 persons. Chronic antipsychotic users were defined and followed up for a switch in antipsychotic treatment within the first period that RLAI was on the market. Multivariable analysis was performed to relate patient, prescriber, and medication characteristics to prescription of a new antipsychotic drug.

Results: Predictors for switching to depot versus oral antipsychotics were male sex, previous use of depot antipsychotics, recent anticholinergic drug use, and a gap in antipsychotic dispensation history. Predictors for switching to RLAI versus FGA depot were previous use of depot and consulting a specialist.

Conclusions: The results suggest that, compared with oral antipsychotics, patients receiving a depot are less compliant users, with more extrapyramidal side effects. Compared with FGA depot, patients receiving RLAI tend to be more severely ill patients. We conclude that RLAI may be partly channeled to patients as a last resort, which may have important consequences for the interpretation of observational effectiveness comparisons between RLAI and other antipsychotics in daily practice.

(*J Clin Psychopharmacol* 2008;28:625–630)

Schizophrenia, with a lifetime prevalence of approximately 1.0%,¹ is one of the most devastating mental illnesses

with severe physical, social, and economic consequences.² Primary cost drivers in schizophrenia are relapse and re-hospitalization and are closely related to low compliance with therapy.^{3–6}

Since the introduction in the 1950s of the now called first-generation antipsychotics (FGAs), medication is the cornerstone in the treatment of schizophrenia. Second-generation antipsychotics (SGAs), which were developed in the 1990s, were initially believed to be superior in medication adherence because of their lower rate of neurological side effects.⁷ Meta-analyses have shown that, with SGAs, dropout rates are not lower than with first-generation ones.⁸ The supposed superiority may partly be based on registration studies that compare SGA with higher than nowadays recommended doses of FGAs.^{8,9} The rates of relapse are modestly but significantly lower with the newer second-generation drugs.¹⁰

A depot antipsychotic aims at promoting compliance in people with particularly severe mental illnesses, thereby enhancing relapse prevention.^{11–16} Several studies showed advantages of a depot regarding rates and durations of re-hospitalization compared with oral antipsychotics.¹¹ Guidelines recommend considering depot antipsychotics in patients with repeated nonadherence.¹⁷ Until the 2000s, only FGAs, such as haloperidol and zuclopenthixol, were available as long-acting depots. Risperidone long-acting injectable (RLAI) is the first and, at the time of our study, only SGA in depot formulation and is available in the Netherlands since May 2003.

In the efficacy studies on RLAI, the type of patients may have represented a selection of the population that will eventually be treated in routine clinical practice. Therefore, it is largely unknown what the real-life benefits and risks are compared with other antipsychotics with similar indications. Such postmarketing comparisons between medications are almost always made using observational study designs. Consequently, adjustment for the type of patients who receive the medications under study is essential for reasons of validity. In addition, models used for pharmacoeconomic evaluation were often based on assumptions rather than actual data about drug prescription in daily practice.^{18,19} Thus, questions about the type of patients who are actually treated with RLAI need to be answered.

The aim of the present study was 2-fold. First, we aimed to determine predictors for the prescription of depot versus oral antipsychotics in patients who had a medication switch during long-term antipsychotic treatment. Second,

*Department of Epidemiology, University Medical Center Groningen, †Groningen Research Institute of Pharmacy, and ‡Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Received March 3, 2008; accepted after revision July 24, 2008.

Address correspondence and reprint requests to Jelle Vehof, MSc, Department of Epidemiology, University Medical Center Groningen, Postbus 30.001, 9700 RB Groningen, the Netherlands. E-mail: j.vehof@student.rug.nl.

Copyright © 2008 by Lippincott Williams & Wilkins

ISSN: 0271-0749/08/2806-0625

DOI: 10.1097/JCP.0b013e31818a6d10

within the patients receiving a depot antipsychotic, we aimed to determine predictors for the prescription of RLAI versus FGA depot. For the analyses of these predictors, data on pharmacy-based prescription drug histories from the target population were used.

MATERIALS AND METHODS

The present study was performed using data from the InterAction DataBase (www.iadb.nl). This database provides anonymous data on drug prescription from 53 pharmacists in a dynamic population of approximately 500,000 residents of the northern and eastern provinces of the Netherlands from 1994 onward. Besides demographical data, such as date of birth and sex, several aspects of pharmacotherapy can be derived from the prescription records. Diagnoses are not included in this database.

Chronic users of antipsychotics were included in the study population. In InterAction DataBase, men and women younger than 65 years on May 1, 2001, were defined as chronic users if they received at least 1 prescription for an

antipsychotic drug in each year of the 2-year period from May 1, 2001, to April 30, 2003. By doing so, we aimed to include representatives of our target population, that is, chronic schizophrenic patients. Because the actual diagnoses were unknown, we tried to achieve this by making restrictions as to age and comedication. A maximum age was set to exclude elderly getting antipsychotic drugs for indications other than schizophrenia, for example, delirium. A lower age limit was set at 12 years to prevent inclusion of children treated with antipsychotics for, among others, attention-deficit/hyperactivity disorder. Lithium users were excluded to exclude patients with bipolar disorder.

We followed up chronic antipsychotic users over time from May 1, 2003, until December 31, 2005, for a switch to a not previously used oral antipsychotic or depot antipsychotic, the latter being FGA depot or RLAI. A switch to a not previously used specific antipsychotic was defined if the first prescription of that antipsychotic occurred from May 1, 2003, onward, and was not prescribed in the period May 1, 2001, to April 30, 2003. The oral and depot preparations of a specific

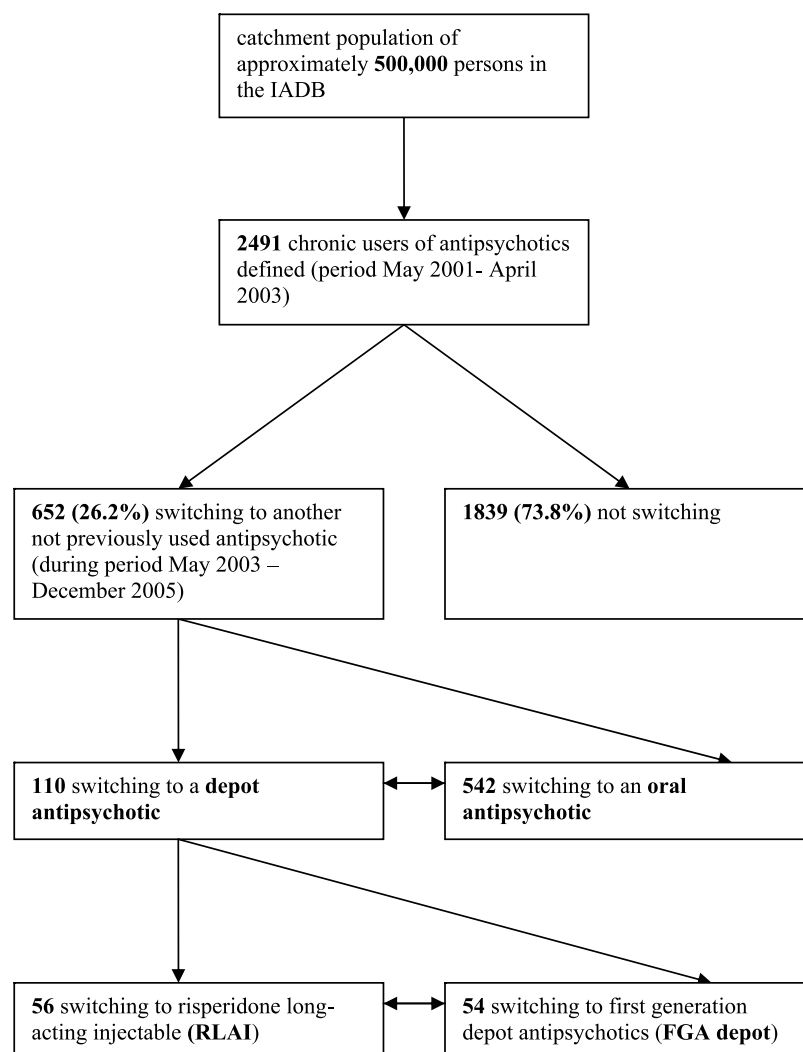


FIGURE 1. Flowchart of the study population, including the 2 comparisons of the study: depot versus oral antipsychotics, and RLAI versus first-generation depot antipsychotics (FGA depot).

TABLE 1. Frequency of the Characteristics of Switchers to Oral and to Depot Antipsychotics

	Oral Antipsychotic (n = 542)		Depot Antipsychotic (n = 110)		RLAI (n = 56)		FGA Depot (n = 54)	
	n	%	n	%	n	%	n	%
Sex								
Female	247	45.6	43	39.1	22	39.3	21	38.9
Age category, yrs								
<30	103	19.0	26	23.6	15	26.8	11	20.4
30–50	313	57.7	49	44.5	20	35.7	29	53.7
51+	126	23.2	35	31.8	21	37.5	14	25.9
Prescriber								
GP	153	28.2	25	22.7	6	10.7	19	35.2
Specialist	389	71.8	85	77.3	50	89.3	35	64.8
3 mo preceding new antipsychotic								
Comedication								
Use of sedatives/hypnotics	135	24.9	17	15.5	10	17.9	7	13.0
Use of anxiolytics	222	41.0	37	33.6	18	32.1	19	35.2
Use of antidepressants	216	39.9	22	20.0	12	21.4	10	18.5
Any of psychotropic medication above	348	64.2	49	44.5	25	44.6	24	44.4
Use of anticholinergics	59	10.9	32	29.1	19	33.9	13	24.1
2 yrs preceding new antipsychotic								
Prior use of depot	41	7.6	37	33.6	25	44.6	12	22.2
No. different antipsychotics used								
1	361	66.6	61	55.4	31	55.3	30	55.6
2 or more	181	33.4	49	44.6	25	44.7	24	44.4
Gap of ≥3 mo	216	39.9	69	62.7	32	57.1	37	68.5

Depot users are divided in RLAI and first-generation depot antipsychotics (FGA depot).

antipsychotic drug were analyzed as different antipsychotics. Thus, a patient who always used oral haloperidol and switched to haloperidol depot after May 1, 2003, was considered as switching to a not previously used antipsychotic, that is, FGA depot. The first prescription date of the new treatment was defined as the index date. In case of more than 1 switch to a new antipsychotic drug per patient in the follow-up period, one of these treatments was randomly selected for the analysis. One-time use of the corresponding oral formulation just before a depot antipsychotic was started, which is common when starting a depot antipsychotic, was not counted as a switch to a new oral antipsychotic.

For each new user, we assessed several potential predictors of use. First, we assessed sex, age at index date, and the prescriber who initiated the new treatment (general practitioner [GP] or specialist). Second, as a marker for recent disease severity, use of psychotropic comedication (anxiolytics [ATC N05B], hypnotics/sedatives [ATC N05C], and antidepressants [ATC N06A]) and, as a marker for extrapyramidal side effects, use of anticholinergic drugs (ATC N04A) were determined in the 3 months preceding the index date. Third, in the 2 years preceding the index date, the number of different antipsychotic drugs used, use of depot antipsychotics, and the presence of a gap of 3 months or more in antipsychotic dispensing history were determined. A gap of 3 months or more in dispensing occurrences of antipsychotic drugs was used as a measure for reduced com-

pliance. The size of the gap was based on the fact that antipsychotics are prescribed for, at most, 3 months in the Netherlands.

We first studied potential predictors of a switch to an oral antipsychotic as compared with a switch to a depot antipsychotic. Next, within the group of depot users, we studied predictors of a switch to RLAI as compared with a switch to FGA depot. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated as measures of relative risk. Multivariable logistic regression analysis was used to adjust for age and sex. Of note is that, in this study, predictors of switching to a new therapy itself are ruled out because the results are conditional on switching.

RESULTS

We identified a total of 2491 eligible subjects as chronic antipsychotic users, and they formed our study cohort. During observation period, a total of 652 users (26.2%) switched to a not previously used antipsychotic drug. Forty patients (6.1%) of these 652 switched to an oral as well as a depot antipsychotic. After random assignment of the patients who switched more than once, 110 patients were classified as switching to a depot antipsychotic, and 542 patients were classified as switching to an oral antipsychotic. Figure 1 shows a flowchart describing the study population.

TABLE 2. Predictors for Switching to (1) a New Treatment With a Depot Versus an Oral Antipsychotic and (2) a New Treatment With RLAI Versus FGA Depot in Chronic Antipsychotic Users

	Depot (n = 110) vs Oral Antipsychotics (n = 542)				RLAI (n = 56) vs FGA Depot (n = 54)			
	Univariable		Multivariable		Univariable		Multivariable	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sex								
Female	0.54	0.35–0.82			1.02	0.47–2.19		
Age category, yrs								
<30	1.0				1.0			
30–50	0.62	0.37–1.05			0.51	0.19–1.33		
51+	1.10	0.62–1.95			1.10	0.39–3.08		
Prescriber								
GP	1.0		1.0		1.0		1.0	
Specialist	1.34	0.82–2.17	1.44	0.88–2.36	4.52	1.64–12.50	4.88	1.72–13.70
3 mo preceding new antipsychotic								
Comedication								
Use of sedatives/hypnotics	0.55	0.32–0.96	0.62	0.35–1.10	1.46	0.51–4.16	1.32	0.42–4.11
Use of anxiolytics	0.73	0.48–1.12	0.78	0.51–1.21	0.87	0.40–1.93	0.87	0.39–1.96
Use of antidepressants	0.38	0.23–0.62	0.41	0.25–0.68	1.20	0.47–3.06	1.11	0.43–2.93
Any of psychotropic medication above	0.45	0.30–0.68	0.49	0.32–0.75	1.00	0.48–2.14	1.00	0.48–2.14
Use of anticholinergics	3.36	2.05–5.50	3.52	2.12–5.84	1.62	0.70–3.73	1.78	0.75–4.23
2 yrs preceding new antipsychotic								
Prior use of depot	6.19	3.73–10.29	5.78	3.44–9.71	2.82	1.23–6.47	2.76	1.17–6.49
No. different used antipsychotics								
1	1.0		1.0		1.0		1.0	
2 or more	1.60	1.06–2.43	1.63	1.07–2.48	1.00	0.48–2.14	0.99	0.46–2.13
Gap of ≥3 mo	2.54	1.66–3.88	2.49	1.62–3.85	0.75	0.24–2.33	0.63	0.28–1.45

Multivariable analysis was corrected for age and sex. Statistically significant predictors are shown in bold font.

Risperidone long-acting injectable accounted for approximately half (n = 56) of all new depot users. From the new users of FGA depot (n = 54), zuclopenthixol (n = 20) was the most frequently dispensed depot antipsychotic, followed by haloperidol (n = 12), flupenthixol (n = 10), fluphenazine (n = 6), perphenazine (n = 3), bromperidol (n = 2), and fluspirilene (n = 1). Table 1 summarizes the characteristics of the new users of the different groups of antipsychotics.

In Table 2, ORs for the predictors of new users of depot antipsychotics as compared with new users of oral antipsychotics are displayed. The age and prescriber distribution did not differ significantly between these users. Compared with new users of oral antipsychotics, users of depot antipsychotics less often were female (OR, 0.54; 95% CI, 0.35–0.82) and more often received an anticholinergic drug before the index date (OR, 3.52; 95% CI, 2.12–5.84). Depot antipsychotics were approximately 2 times less frequently prescribed to patients who recently used psychotropic comedication (OR, 0.49; 95% CI, 0.32–0.75), especially antidepressants (OR, 0.41; 95% CI, 0.25–0.68). Depot antipsychotics were more often prescribed to patients who had a gap of 3 or more months in their prescription data (OR, 2.49; 95% CI, 1.62–3.85). Finally, depot antipsychotics were around 6 times

more frequently prescribed to patients who had been prescribed a depot antipsychotic before (OR, 5.78; 95% CI, 3.44–9.71) and to patients in which the number of different used oral antipsychotics before was higher (OR, 1.63; 95% CI, 1.07–2.48).

Also in Table 2, ORs from the predictors of new users of RLAI as compared with new users of FGA depot are shown. Compared with FGA depot, RLAI was more often prescribed by specialists (OR, 4.88; 95% CI, 1.72–13.70) and to patients who had been prescribed a depot before (OR, 2.76; 95% CI, 1.17–6.49). There was no significant difference in the other characteristics.

DISCUSSION

In our study, chronic antipsychotic drug users who switched to a depot formulation, more often were male, had more frequently used anticholinergic drugs before, had less often used psychotropic comedication before, and had more gaps in their antipsychotic prescription history compared with those who switched to an oral antipsychotic. Furthermore, depot antipsychotics were predominantly prescribed to patients who had used depot antipsychotics before. Users of RLAI had similar profiles as FGA depot users, except for 2 characteristics. Patients who used a depot antipsychotic

before, and who consulted a psychiatrist rather than a GP, were more likely to be prescribed RLAI than FGA depot.

Some potential limitations of our study should be mentioned. We used gaps of 3 months or more in antipsychotic drug history as a proxy for medication compliance. This is, however, a somewhat dual parameter, because it can point to noncompliance or it can point to (re)hospitalization. Data of hospital prescriptions, however, were not available. Nevertheless, both causes of a gap indicate deterioration of the patient. Another reason for a gap in prescription could be the result of “targeted treatment” in which a patient stops his medication after a certain psychosis-free period and starts again when he or she has a new psychosis. A gap from this cause may be indicative of a temporary improvement of the patient. However, we consider a gap of 3 months or more on average being a measure of noncompliance. Unfortunately, unambiguous information on compliance to therapy and underlying disease cannot be derived from pharmacy prescription data. Furthermore, we were unable to assess other relevant prognostic clinical characteristics such as the number of prior psychotic episodes, direct clinical measures such as the Clinical Global Impression scale or Positive and Negative Syndrome Scale, or the reason for switching. Although we had no data on the diagnoses of the patients in our study, the far majority must have been experiencing schizophrenia.²⁰ Finally, we limited the study population to those subjects receiving antipsychotic medication during a 2-year period to select chronic users. Because first-episode patients who have been clinically stable for 1 year may have undergone a trial of discontinuation of antipsychotics, which is put forward as an option in Dutch guidelines, these patients may be underrepresented in our study.

Our results indicate that depot antipsychotics are prescribed to patients who had adherence problems toward their oral medication and more frequent or more severe extrapyramidal side effects. These findings are in line with our a priori expectations. First, following the guidelines,¹⁷ extrapyramidal side effects are one of the main reasons to change antipsychotic treatment. One of the possible benefits of a depot antipsychotic is that a stable, low dose can be sustained, with less side effects as a result.^{16,21} Indeed, the higher prescription rate of anticholinergics in the 3 months before the switch in users of depot is in line with this notion. Second, a gap in prescription history may be a sign of noncompliance, which is the main reason to switch to a depot antipsychotic. With a depot antipsychotic, compliance to therapy can be improved.^{11–15} Thus, a higher number of prescription gaps is what we expected in the group of new users of depot antipsychotics compared with oral antipsychotics. Interestingly, male patients are also more likely to be prescribed depot antipsychotics than female patients. An explanation could be that men with schizophrenia have a poorer prognosis and outcome than women,¹ needing more different medication strategies. It can be hypothesized that men are thought to have a lower compliance than women, although this cannot be confirmed by empirical evidence.²² One could expect that new users of depot antipsychotics are not only less compliant patients but also more severely ill

patients than new users of oral antipsychotics. However, this expectation was not supported by our data because the use of psychotropic comedication was not associated with switching to depot antipsychotics.

The difference in prior use of depot between RLAI and FGA depot users suggests that RLAI is especially prescribed to patients not responding satisfactorily to FGA depot, the latter being suggestive of more severe illness. Also, patients with schizophrenia treated with first-generation depot antipsychotics have been shown to use more alcohol and illicit substances and to show higher levels of psychopathology.²³ Our finding that switching to RLAI is more likely than to FGA depot when a specialist is the prescriber is also in line with channeling of RLAI to the more severely ill patients. An alternative explanation for the difference in prescriber between FGA depot and RLAI that cannot be excluded is that specialists were more familiar with the existence of RLAI after its introduction than were GPs. Also corroborating our findings is the study of Niaz and Haddad,²⁴ where patients prescribed RLAI had significantly higher baseline rates of drug misuse, unemployment, and forensic markers than control patients prescribed oral antipsychotics. The increasing evidence suggesting that RLAI is channeled to the more severely ill patient may have important consequences for the validity of comparisons between RLAI and other groups of antipsychotics in observational studies.²⁵

In our study, a relatively small number of chronic antipsychotic users switched to a depot antipsychotic. This concurs with observations by others^{21,26} that depot antipsychotics, despite their potential advantages, are still not much prescribed in the treatment of schizophrenia. This limited use of depot antipsychotic medication may be due to the introduction of the oral SGAs in the 1990s,²¹ leading to a less awareness of its diminished relapse rates, its reduced durations of hospitalizations,^{11,16} and its well acceptance by experienced patients.²⁷ Heres et al²⁶ showed in their study on attitudes of psychiatrists toward antipsychotic depot medication that the main reason not to choose a FGA depot was the fear of extrapyramidal side effects. The main reason for not prescribing RLAI was the assumed sufficient compliance with an oral SGA.

In conclusion, depot antipsychotics are preferentially prescribed to patients with adherence problems and more extrapyramidal side effects, as compared with oral antipsychotics. This is in accordance with therapeutic guidelines.¹⁷ Our data further indicate that, within depot users, RLAI is largely channeled to the more severely ill patients who tried a depot before, that is, RLAI is used as a last resort for many users. These observations could have important consequences for interpreting observational comparisons between groups of antipsychotics.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest or support.

REFERENCES

1. Mc Grath J, Saha S, Welham J, et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of

- schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med.* 2004;2:13.
2. Knapp M. Costs of schizophrenia. *Br J Psychiatry.* 1997;171:509–518.
 3. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophr Bull.* 1995;21:419–429.
 4. Rice DP. The economic impact of schizophrenia. *J Clin Psychiatry.* 1999;60:4–6.
 5. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. *Schizophr Bull.* 2004;30:279–293.
 6. Buckley PF. Treatment of schizophrenia: let's talk dollars and sense [correction appears in *Am J Manag Care* 1998;4:611]. *Am J Manag Care.* 1998;4:369–383.
 7. Schultz SH, North SW, Cleaveland GS, et al. Schizophrenia: a review. *Am Fam Physician.* 2007;75:1821–1829.
 8. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ.* 2000;321:1371–1376.
 9. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet.* 2003;361:1581–1589.
 10. Leucht S, Barnes TR, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry.* 2003;160:1209–1222.
 11. Davis JM, Matalon L, Watanabe MD, et al. Depot antipsychotic drugs. Place in therapy. *Drugs.* 1994;47:741–773.
 12. Weiden P, Glazer W. Assessment and treatment selection for 'revolving door' inpatients with schizophrenia. *Psychiatr Q.* 1997;68:377–392.
 13. Dencker SJ, Axelsson R. Optimising the use of depot antipsychotics. *CNS Drugs.* 1996;6:367–381.
 14. Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry.* 1992;53:426–433.
 15. Davis JM, Kane JM, Marder SR, et al. Dose response of prophylactic antipsychotics. *J Clin Psychiatry.* 1993;54:24–30.
 16. Kane JM, Aguglia E, Altamura AC, et al. Guidelines for depot antipsychotic treatment in schizophrenia. *Eur Neuropsychopharmacol.* 1998;8:55–66.
 17. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. *Am J Psychiatry.* 2004;161:1–56.
 18. Edwards NC, Locklear JC, Rupnow MF, et al. Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. *Pharmacoeconomics.* 2005;23:75–89.
 19. Heeg BM, van Aalst G, van den Arend U, et al. A discrete events model of long term outcomes and costs of treatment with long-acting risperidone in schizophrenia [abstract no. PMH5]. *Value Health.* 2002;5:515–516. Poster also presented at the International Society for Pharmacoeconomics and Outcomes Research 5th Annual European Congress; November 3–5, 2002; Rotterdam, the Netherlands.
 20. Rijken CA, Boelema GJ, Slooff CJ, et al. Off-label use of antipsychotics in the community pharmacy: the sex differences. *Pharmacopsychiatry.* 2003;36:187–191.
 21. Patel MX, David AS. Why aren't depot antipsychotics prescribed more often and what can be done about it? *Adv Psychiatr Treat.* 2005;11:203–213.
 22. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63:892–909.
 23. Shi L, Ascher-Svanum H, Zhu B, et al. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. *Psychiatr Serv.* 2007;58:482–488.
 24. Niaz OS, Haddad PM. Thirty-five months experience of risperidone long-acting injection in a UK psychiatric service including a mirror-image analysis of in-patient care. *Acta Psychiatr Scand.* 2007;116:36–46.
 25. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. *Stat Med.* 1991;10:577–581.
 26. Heres S, Hamann J, Kissling W, et al. Attitudes of psychiatrists toward antipsychotic depot medication. *J Clin Psychiatry.* 2006;67:1948–1953.
 27. Walburn J, Gray R, Gournay K, et al. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Br J Psychiatry.* 2001;179:300–307.